GENERAL GYNECOLOGY

Oral progestogens vs levonorgestrel-releasing intrauterine system for endometrial hyperplasia: a systematic review and metaanalysis

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OBJECTIVE: To conduct a systematic review and metaanalysis of studies evaluating the regression rate of endometrial hyperplasia with oral progestogens and levonorgestrel-releasing intrauterine system.

STUDY DESIGN: Searches were conducted on Medline, Embase, Cochrane Library, and Web of Science, and reference lists of relevant articles were examined. The methodologic index for nonrandomized studies was used for quality assessment. Metaanalysis was performed with random effects model.

RESULTS: There were 24 observational studies (1001 women), of low methodologic quality, evaluating the outcome of regression of endometrial hyperplasia with oral progestogens or levonorgestrel-releasing intrauterine system. Metaanalysis showed that oral progestogens achieved a lower pooled regression rate compared with levonorgestrel-releasing intrauterine system for complex (pooled rate, 66% vs 92%; $P < .01$) and atypical hyperplasia (pooled rate, 69% vs 90%; $P = .03$). There was no statistical difference in simple hyperplasia (pooled rate, 89% vs 96%; $P = .41$).

CONCLUSION: Oral progestogens appear to induce a lower disease regression rate than Levonorgestrel-releasing intrauterine system in the treatment of endometrial hyperplasia.

Key words: endometrial hyperplasia, LNG-IUS, observational studies, progestogens

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Endometrial hyperplasia is a common diagnosis (5-10%) in women presenting with abnormal uterine bleeding, and can progress to cancer if left untreated.[1] The risk of progression of endometrial hyperplasia to cancer is dependent on the histologic diagnosis. The risk of cancer progression is low for women with complex nonatypical endometrial hyperplasia (3%) compared with women with cytologic atypia (8-29%).[2] Nonsurgical therapeutic strategies in endometrial hyperplasia aim to induce disease regression and prevent progression to cancer. These strategies, if successful, could reduce the number of hysterectomies performed for this condition and hence reduce morbidity and health care costs.

Currently, there are no professional body guidelines for the management of endometrial hyperplasia. The use of progestogens, which antagonize the estrogen effect on the endometrium, can induce endometrial regression, and prevent progression to cancer. The main progestational agents used to treat endometrial hyperplasia are oral progestogens (norethisterone acetate, megestrol acetate, and medroxyprogesterone 17-acetate). More recently, the levonorgestrel-releasing intrauterine system (LNG-IUS; Mirena; Schering Health Care, Burgess Hill, UK) developed primarily as a contraceptive device, has also been used successfully to treat endometrial hyperplasia. This system has been proven to achieve higher concentrations of progestogens in the endometrium by almost 100-fold compared with oral administration.[3] As it is not user dependent, compliance is 100%. We conducted a systematic review of studies evaluating oral and intrauterine progestogens for the treatment of endometrial hyperplasia and metaanalyzed their treatment effects.

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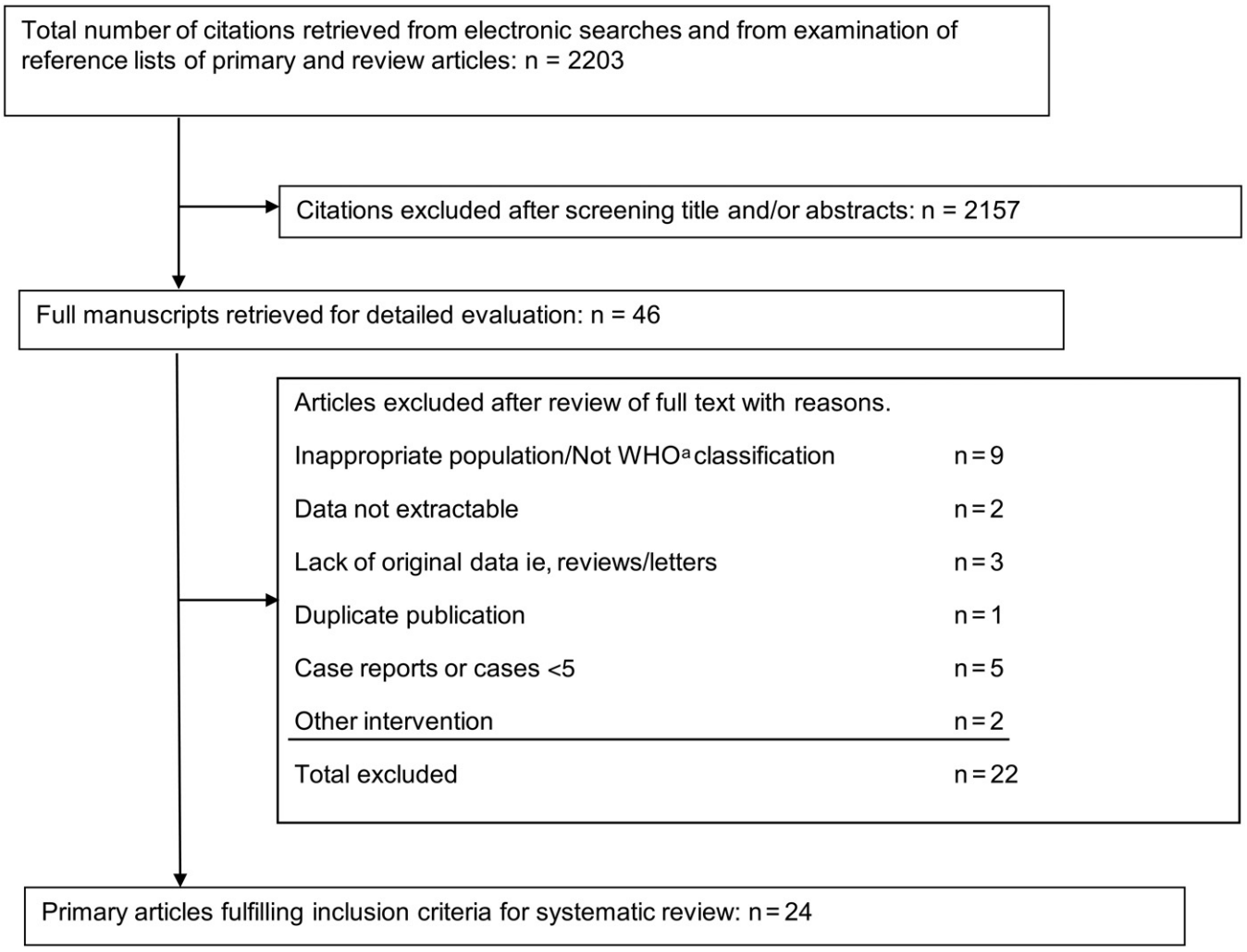
Materials and Methods

Identification of literature

The population of interest in this systematic review was women with endometrial hyperplasia, the intervention was treatment with oral progestogens, the comparison was LNG-IUS, and the outcome was evidence of disease regression or persistence. The following electronic databases were searched: MEDLINE (1950 to December 2009), EMBASE (1980 to December 2009), Cochrane Central Register of Controlled Trials, and Web of Science conference proceedings (ISI Proceedings, 1990 to December 2009). A combination of Medical Subject Headings (MeSH) and text words

FIGURE 1
Study selection process



Study selection process for systematic review of oral and intrauterine progestogens for the treatment of endometrial hyperplasia.

[a] World Health Organization Classification.

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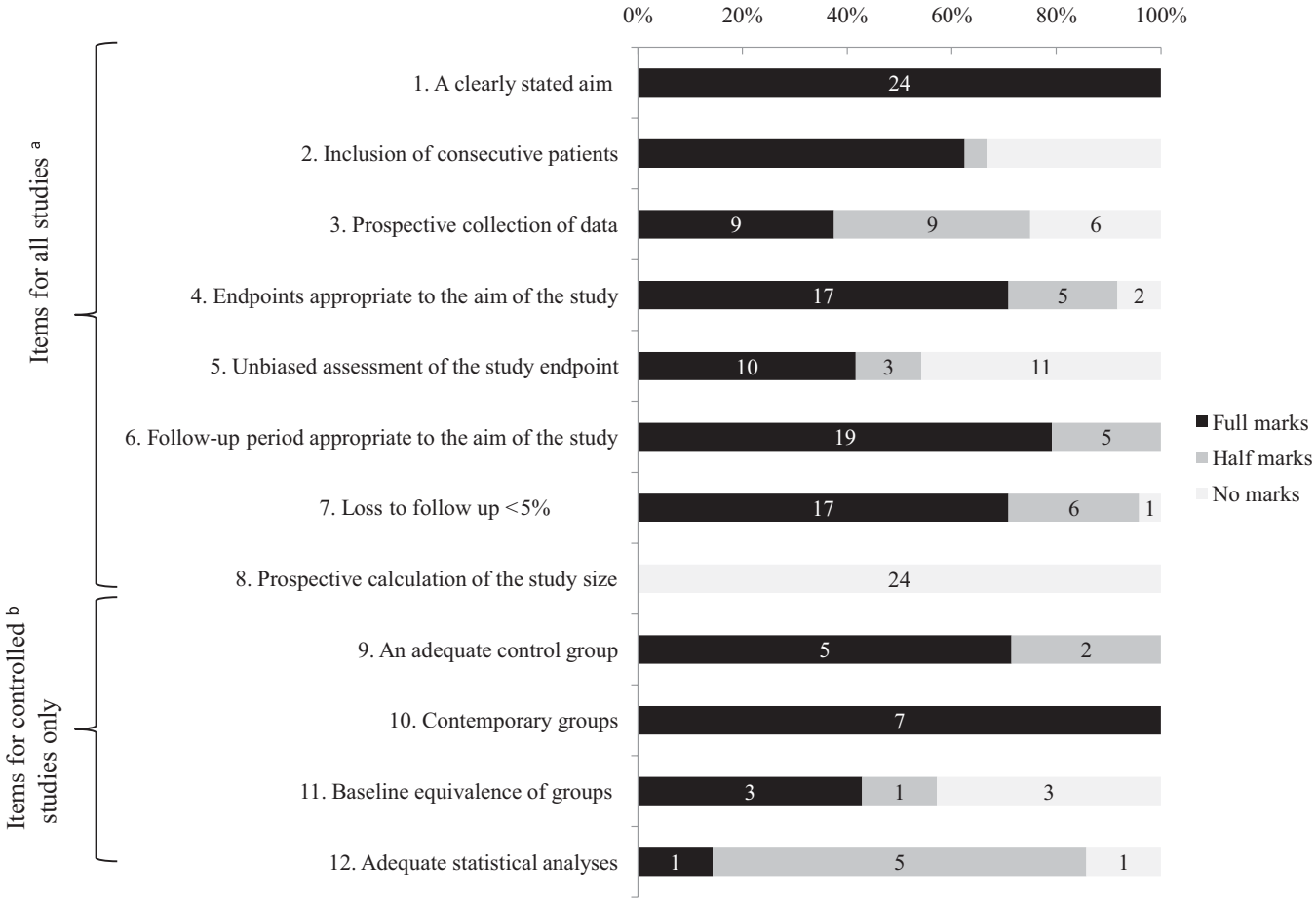
were used to generate 2 subsets of citations, one including studies of endometrial hyperplasia ("endometr* hyperplas*", "premalignant endometr*", "precancer* endometr*") and the other including studies of progestogens and intrauterine devices or systems ("intrauterine devices medicated", "Levonorgestrel", "mirena", "intrauterine progest*", "LNG-IU*", "progest*", "gestag*"). These subsets were combined with "AND" and limited to "Humans and Female" to generate a subset of citations relevant to our research question. The reference lists of all known primary and review articles were examined to identify cited articles not captured by electronic searches. Language or geographical restrictions were not applied during search or selection. The searches were conducted independently by I.D.G and T.K.P.

Study selection and data extraction

Studies were selected if the participants were women diagnosed histologically with endometrial hyperplasia, the intervention was treatment with either oral progestogens or LNG-IUS, and the outcome was histologic disease regression rates, as assessed on endometrial biopsy or hysterectomy specimen. Both controlled and uncontrolled designs were included. Case reports or series with <5 cases were excluded. Studies reporting on women with endometrial hyperplasia treated with other form of progestogens than oral or LNG-IUS (eg, injectable, pessaries) were excluded. Studies classifying women with endometrial hyperplasia in other than the World Health Classification of 1994 (simple, complex, and atypical) were also excluded.

Studies were selected in a 2-stage process. First, the titles and abstracts from the electronic searches were scrutinized by 2 reviewers independently (I.D.G. and M.S.) and full manuscripts of all citations that met the predefined selection criteria were obtained. Secondly, final

FIGURE 2
Quality checklist



Quality checklist of the studies included in the systematic review of oral and IUS progestogens for the treatment of endometrial hyperplasia.

[a]Quality items for observational studies with or without an active control group; [b]Additional quality items for observational studies with an active control group.

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inclusion or exclusion decisions were made on examination of the full manuscripts. In cases of duplicates, the most recent or the most complete publication was used. Any disagreements about inclusion were resolved by consensus or arbitration by a third reviewer (A.C.).

Two reviewers (I.D.G. and M.S.) completed the quality assessment. The Methodologic Index for NonRandomized Studies (MINORS), which assesses the quality of the included studies, was implemented.[4] Items assessed included selection of cases or cohorts and controls, comparability and information on exposure and outcome. This index was preferred over Newcastle-Ottawa Quality Assessment Scale[5] as we included studies without a control group and the MINORS checklist allows a quality evaluation in studies with and without a control group. From each study, outcome data were extracted in 2×2 tables by the 2 reviewers I.D.G. and M.S. No ethical approval was sought for this study as it was a systematic review and metaanalysis of published articles.

Statistical analysis

Regression rates from individual studies were metaanalyzed using a random effects model.[6] Heterogeneity of the exposure effects was statistically analysed using the χ^2 test.[7] Exploration of the causes of heterogeneity was planned using variation in features of population, exposure, and study quality.[8] The regression rates between the 2 interventions (oral progestogens and LNG-IUS) were compared with the aid of metaregression. Statistical analyses were performed using Stata 8.0 (Stata Corp, College Station, TX).

RESULTS

The search strategy yielded 2203 citations all captured from electronic citations. Of these, 2157 were excluded as it was clear from the title and abstract that they did not fulfill the selection criteria. Examination of the full manuscripts of the remaining 46 articles found that 3 studies lacked original data (eg, reviews or letters), 1 study was a duplicate, and 18 studies did not meet the selection criteria. Thus, a total of 24 primary studies, including 1001 women with endometrial hyperplasia were selected for this review (Figure 1). The longest follow-up period

TABLE
Characteristics of the studies

Author	Type of study	Study population	Intervention or study groups	Outcome and follow-up
Bese, et al[9] (n = 37)	Matched controlled study	Simple hyperplasia (n = 19) and matched controls without hyperplasia (n=18)	Norethisterone 15 mg/d for 10 d between the 16th and 25th d for 3 mo	Outcome: histologic response at 3 mo, proliferative and apoptotic activity Follow-up: 3 mo
Buttini, et al[10] (n = 57)	Retrospective comparative study	Women with simple (n = 33), complex (n = 8), or atypical hyperplasia (n = 16)	Oral progestogens, usually Medroxyprogesterone 10-20 mg/d of unreported duration and regimen (n = 10), LNG-IUS[a] followed by hysterectomy (n = 7), LNG-IUS[a] alone (n = 19), and hysterectomy alone (n = 21)	Outcome: histological response at 6 mo and menstrual function Follow-up: variable; range, 6–69 mo
Clark, et al[11] (n = 281)	Retrospective comparative study	Women with simple (n = 55), complex (n = 173) or atypical hyperplasia (n = 53) Excluded: women with incidental finding of hyperplasia diagnoses on hysterectomy specimens	Oral progestogens of unreported type, dose, duration and regimen (n = 77), LNG-IUS (n = 29), HRT (n = 2), other medical (n = 2), endometrial ablation (n = 2), hysterectomy (n = 109), and observation only (n = 60)	Outcome: histologic and clinical response Follow-up: mean of 36 mo; range, 24–48
Guven, et al[12] (n = 27)	Case series study	Women with simple (n = 16), complex (n = 5), or atypical hyperplasia (n = 3)	Megestrol 160-320 mg/d for 3 mo (n = 22), 45 d (n = 2), or 60 d (n = 3)	Outcome: histologic response every 3-6 mo Follow-up: not reported
Haimovich, et al[13] (n = 15)	Prospective case series study	Women with simple hyperplasia (n = 15) Excluded: women with uterine hypertrophy or submucosal myomas	LNG-IUS for 24 mo	Outcome: histologic response and bleeding pattern at 3, 6, 12, and 24 mo Follow-up: 24 mo
Horn, et al[14] (n = 502)	Retrospective controlled study	Women with complex (n = 208) or atypical hyperplasia (n = 7) that received progestogens and women treated without progestogens (n = 287) Excluded: women with no clinical data regarding follow-up, women reclassified into simple hyperplasia after histologic re-examination and women with synchronous cancer	Medroxyprogesterone or norethisterone for 3-5 mo. Norethisterone 5 mg/d for premenopausal women, Medroxyprogesterone 10 mg/d for perimenopausal women and 20-50 mg/d for postmenopausal women (n = 215)	Outcome: histologic response at a median of 4.8 mo; range, 3–22 Follow-up: not reported
Jarvela and Santala[15] (n = 34)	Oral progestogen arm of a randomized controlled trial	Women with simple (n = 16) or complex hyperplasia (n = 1) that received progestogens and women treated with thermal balloon endometrial ablation (n = 17) Excluded: women with previous progestogen use, signs of atypical hyperplasia, pregnancy, desire for fertility, fibroids >3 cm or distorting the uterine cavity, genital infections, malignancy or previous endometrial ablation	Group 1: for premenopausal women, medroxyprogesterone 10 mg/d from day 15-24 for 3 mo and for postmenopausal women medroxyprogesterone, 10 mg/d for 3 mo (n = 17) Group 2: endometrial ablation (n = 17)	Outcome: histologic response, clinical and ultrasound examination at 6 and 12 mo Follow-up: not reported

Gallos. Oral progestogens vs LNG-IUS for endometrial hyperplasia. Am J Obstet Gynecol 2010. *(continued)*

TABLE
Characteristics of the studies *(continued)*

Author	Type of study	Study population	Intervention or study groups	Outcome and follow-up
Jobo, et al[16] (n = 53)	Retrospective comparative study	Women with complex aypical hyperplasia (n = 53) Excluded: women who refused treatment and follow-up	Group 1: medroxyprogesterone acetate 10 mg for 14 d/ cycle for 6 mo (n = 8), Group 2: medroxyprogesterone acetate 400 mg/d for 6 mo (n = 12) hysterectomy (n = 30) and observation only (n = 2)	Outcome: histologic response at 10.8 wk (4-30) for group 1 and 7.3 (3-15) wks for group 2 Follow-up: mean of 66 mo; range, 8–281
Kaku, et al[17] (n = 30)	Retrospective case series	Women with atypical hyperplasia (n = 18) or endometrial carcinoma (n = 12) wishing to preserve their fertility Excluded: women were excluded if found not to have atypical hyperplasia or endometrial carcinoma after pathologic review, women were excluded if follow-up specimens were not available	Medroxyprogesterone 100-600 mg/d for 1-23 mo for endometrial hyperplasia and 200-800 mg/d for 2-14 mo for endometrial cancer	Outcome: histologic response and pregnancy rates every 1-4 mo Follow-up: median of 31.5 mo; range, 10–133
Milam, et al[18] (n = 38)	Retrospective case series study	Women with matched preprogesterone and postprogesterone treated pairs of endometrial biopsies with endometrial hyperplasia (n = 38) Excluded: women with disagreement of diagnosis of endometrial hyperplasia after histological re-evaluation and when there was limited material for immunohistochemical evaluation	Medroxyprogesterone, megestrol, or norethisterone for a median of 3 mo (1-12 mo) of unreported dose and regimen	Outcome: histologic and immunohistochemical response Follow-up: not reported
Minaguchi, et al[19] (n = 31)	Case series study	Women with atypical complex hyperplasia (n = 12) or Stage IaG1 carcinoma (n = 19) who wished to preserve fertility or could not receive surgery because of complications Excluded: women over the age of 40 years and those who did not attempt to conceive	Medroxyprogesterone 2.5-600 mg/d for 3-18 mo, mostly 400-600 mg/d for 6 mo	Outcome: histologic and immunohistochemical response every 2-4 mo, pregnancy and hysterectomy rates Follow-up: median of 40.7 mo; range, 2–109
Randall and Kurman[20] (n = 67)	Retrospective case series study	Women under the age of 40 years with atypical hyperplasia (n = 32) or well-differentiated carcinoma (n = 35) Excluded: women who declined treatment and any follow-up and women who declined treatment and endometrial sampling	Oral progestogens Medroxyprogesterone 10-30 mg/d for 3-12 mo or megestrol 40-160 mg/d for 3-12 mo (n = 29), ovulation induction (n = 2), bromocriptine (n = 1), oral contraceptive (n = 1), and hysterectomy (n = 27)	Outcome: histologic response at 3-6 mo, pregnancy and hysterectomy rates Follow-up: mean of 40 mo; range, 9–79
Rattanachaiyanont, et al[21] (n = 134)	Prospective case series study	Women with simple (n = 116) or complex (n = 18) hyperplasia that completed a cycle of progestogens Excluded: women not having progestogen therapy, not having data on endometrial histology, loss to follow-up, pregnancy, and amenorrhea	Mainly cyclic medroxyprogesterone 10 mg/d and norethisterone 10 mg/d for 12-14 consecutive d/ mo for 6 mo	Outcome: histologic response at 4, 16, and 24 wks, vaginal bleeding pattern and associated pelvic pathology Follow-up: not reported

Gallos. Oral progestogens vs LNG-IUS for endometrial hyperplasia. Am J Obstet Gynecol 2010. *(continued)*

TABLE
Characteristics of the studies *(continued)*

Author	Type of study	Study population	Intervention or study groups	Outcome and follow-up
Reed, et al[22] (n = 185)	Retrospective case series study	Women >18 years with complex (n = 115) or atypical (n = 70) hyperplasia after central pathology review and with an additional pathologic specimen 8 wk to 6 mo after index diagnosis Excluded: women with follow-up specimen not available or not diagnostic, dispensed >14 d of estrogen and <14 d of progestogen dispensed	Medroxyprogesterone (n = 66), megestrol (n = 61), or norethisterone (n = 11) at different doses for 14 d up to 6 mo and observation only (n = 38)	Outcome: histologic response at 8 wk up to 6 mo Follow-up: mean of 16.4 wk; range, 8–26
Signorelli, et al[23] (n = 21)	Prospective case series study	Women under the age of 40 years with atypical hyperplasia (n = 10) or endometrial cancer (n = 11) wishing fertility potential	Cyclical natural progesterone 200 mg daily from d 14 to d 25 (n = 21)	Outcome: histologic response and pregnancy rate every 3 mo Follow-up: median of 98 mo; range, 35–176
Tjalma, et al[24] (n = 8)	Case series study	Women with atypical hyperplasia (n = 7) and with endometrial cancer (n = 1)	LNG-IUS	Outcome: histologic and immunohistochemical response at 3-6 mo Follow-up: mean of 29 mo, range, 11–51
Varma, et al[25] (n = 105)	Prospective cohort study	Women with simple (n = 16), complex (n = 80), and atypical hyperplasia (n = 9)	LNG-IUS	Outcome: histologic response, hysterectomy and cancer rates at 3, 6, 12, 18, 24 mo Follow-up: not reported
Vereide, et al[26] (n = 50)	Prospective cohort study	Women with simple (n = 26), complex (n = 11), and atypical (n = 13) hyperplasia	LNG-IUS (n = 21) and oral medroxyprogesterone 10 mg for 10 d per cycle for 3 mo (n = 29)	Histologic and immunohisto-chemical response at 3 mo Follow-up: not reported
Wheeler, et al[27] (n = 44)	Retrospective cohort study	Women with atypical hyperplasia (n = 18) or well-differentiated endometrial cancer (n = 26)	Oral progestogens of unreported type, dose and duration (n = 29) or progesterone-releasing intrauterine device (n = 15)	Outcome: histologic response at 1-3, 4-6, and 7-9 mo Follow-up: median of 11 mo; range was not reported
Wildermeersch, et al[28] (n = 20)	Prospective cohort study	Women with simple (n = 12) or atypical hyperplasia (n = 8)	LNG-IUS 14 μg releasing (n = 7) for 3 y, replaced by a 20 μg releasing LNG-IUS (n = 13)	Outcome: histologic response and ultrasound endometrial thickness Follow-up: mean of 36 mo; Range, 14–90
Witkiewicz, et al[29] (n = 15)	Retrospective case series	Women with atypical hyperplasia (n = 7) or well-differentiated carcinoma (n = 8)	Megestrol for a mean of 13.3 mo (n = 11), megestrol + IUD for a mean of 31 mo (n = 2), megestrol + medroxyprogesterone for 20 mo (n = 1), megestrol + IUD + depot medroxyprogesterone for 33 mo (n = 1). Doses of oral progestogens were not reported.	Outcome: histologic and immunohistochemical response Follow-up: not reported

Gallos. Oral progestogens vs LNG-IUS for endometrial hyperplasia. Am J Obstet Gynecol 2010. *(continued)*

TABLE
Characteristics of the studies *(continued)*

Author	Type of study	Study population	Intervention or study groups	Outcome and follow-up
Yener, et al[30] (n = 30)	Oral progestogens arm of a randomized controlled study	Women with simple hyperplasia (n = 30)	Medroxyprogesterone 20 mg/d from d 16 to d 25 for 3 mo (n = 15) and depot goserelin subcutaneous implant each 28 d for 3 times (n = 15)	Outcome: histologic response at 3 mo Follow-up: not reported
Yu, et al[31] (n = 25)	Retrospective cohort study	Women <35 years with severe atypical hyperplasia (n = 17) or endometrial carcinoma (n = 8)	Medroxyprogesterone 250-500 mg/d for endometrial carcinoma and 100-500 mg/d for atypical hyperplasia (n = 22) or megestrol acetate or hydroxyprogesterone caproate of unreported dose (n = 3), all continued for at least 3-6 mo after remission	Outcome: histologic response at intervals of 3 mo Follow up: mean of 34.6 months; range, 7–114

HRT, hormone replacement therapy; *IUD*, intrauterine device; *LNG-IUS*, levonorgestrel-releasing intrauterine system.

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was 8 years. Fifteen studies were case series and 9 were controlled studies. The main characteristics of the 24 studies and the MINORS Index are presented in Figure 2 and the Table. Although all studies included women with either oral progestogens or LNG-IUS, the type, dose, regimen, and duration of treatment varied. The type of hyperplasia (simple, complex, or atypical) treated also varied between the different studies. Most studies were judged to be of poor quality on the MINORS index (Figure 2), with particular low scores for prospective calculation of the study size, prospective recruitment, and biased assessment of regression rates.

Regression outcomes for simple hyperplasia

Metaanalysis of the 9 studies (213 women) of women with simple hyperplasia treated with oral progestogens showed a pooled regression rate of 89% (95% confidence interval [CI], 77–100) (Figure 3). Pooling the 6 studies (72 women) of women with simple hyperplasia treated with LNG-IUS found a pooled regression rate of 96% (95% CI, 76–100). Metaregression showed that the pooled regression rates were not statistically significantly different ($P = .41$). The P value for the χ^2 test for heterogeneity was .95 for oral progestogens and .99 for LNG-IUS, indicating little variability in regression rates for these studies.

Regression outcomes for complex hyperplasia

Metaanalysis of the 9 studies (389 women) of women with complex hyperplasia treated with oral progestogens showed a pooled regression rate of 66% (95% CI, 58–74). Pooling the 4 studies (102 women) of women with complex hyperplasia treated with LNG-IUS found a pooled regression rate of 92% (95% CI, 65–100). Metaregression showed that the pooled regression rates were statistically significantly different ($P < .01$). The P value for the χ^2 test for heterogeneity was 0.86 for the oral progestogens and 0.99 for LNG-IUS, indicating little heterogeneity in the pooled regression rates.

Regression outcomes for atypical hyperplasia

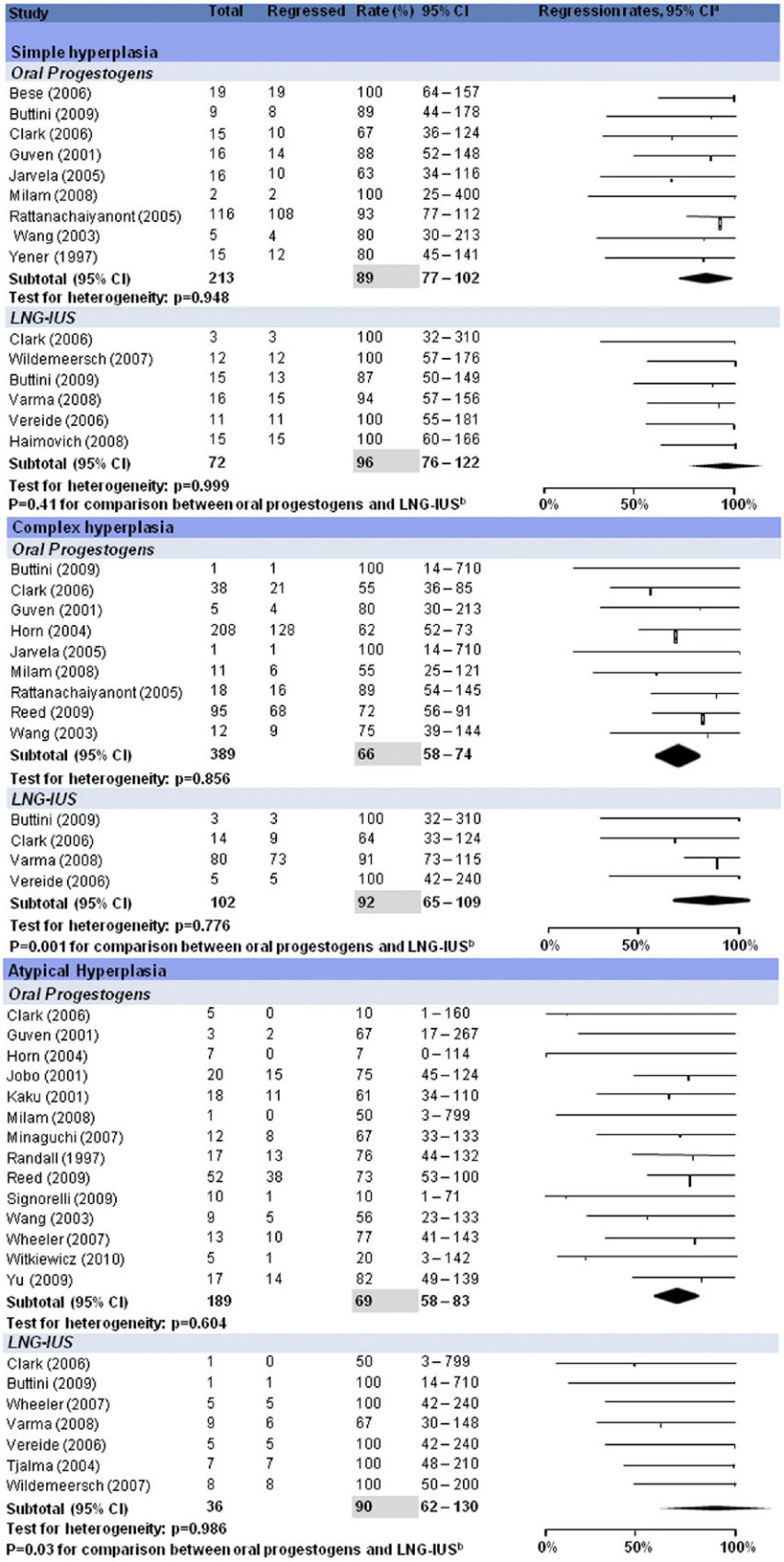
Metaanalysis of the 14 studies (189 women) of women with atypical hyperplasia treated with oral progestogens showed a pooled regression rate of 69% (95% CI, 58–83). Pooling the 7 studies (36 women) of women with atypical hyperplasia treated with LNG-IUS found a pooled regression rate of 90% (95% CI, 62–100). The pooled regression rates were statistically significantly different ($P = .03$). The P value for the χ^2 test for heterogeneity was 0.60 for the oral progestogens and 0.99 for LNG-IUS, indicating little heterogeneity in the pooled regression rates.

COMMENT

This review, which included 1001 women with endometrial hyperplasia, showed that complete regression of endometrial hyperplasia was achieved in a lower proportion of women treated with oral progestogens compared with women treated with LNG-IUS for complex (66% vs 92%) and atypical hyperplasia (69% vs 90%). There was no significant difference found between the 2 treatments for simple hyperplasia (89% vs 96%).

Our study provides an overview of the efficacy of oral progestogens and LNG-IUS for the treatment of endometrial hyperplasia and summarizes the current evidence. It has major clinical relevance to the understanding and treatment of endometrial hyperplasia. We metaanalyzed the disease regression rates for both interventions separately for each type of hyperplasia. This reduced potential het-

FIGURE 3
Metaanalysis of studies



Metaanalysis of studies of oral progestogens vs levonorgestrel-releasing intrauterine system for the treatment of endometrial hyperplasia.

[a]Upper limit of CIs in the forest plot of individual studies has been limited to 100%; [b]Comparison of disease regression rates between oral progestogens and levonorgestrel-releasing intrauterine system was carried out using metaregression analysis.

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erogeneity between the studies and enhanced the clinical applicability of our findings. We also assessed the heterogeneity both graphically using forest plots and statistically. We contacted authors of the primary studies for clarification of relevant information. We used a validated tool (MINORS) to rate the quality of the included studies.

However, the strength of these findings is limited by the dearth of primary literature, unreliability of the data because of the small numbers and the risk of bias in most of the studies because of their poor quality. Furthermore, the interpretation of these findings should also take into account publication bias, which is likely to result in preferential reporting of cases with good outcomes, leading to possible overestimation of effect. It is plausible that different types and doses of oral progestagens may have a differential effect on disease regression rates. However, there is no consistent evidence to suggest such a differential effect from the studies included in our review, as well as a large study by Reed et al,[22] which found that there are no differences in endometrial hyperplasia regression rates between the various oral progestogens.

We believe that the difference in disease regression rates of oral progestogens and LNG-IUS for the treatment of endometrial hyperplasia found in our review may be explained by the mode of progestogen delivery. The progestogen concentrations in the uterine mucosa when delivered through an intrauterine device, directly into the cavity are reported to exceed that of the oral treatment by several-fold.[3] The intrauterine progestogen release is also associated with higher patient satisfaction and, therefore patients are more likely to continue the treatment. This higher chance of patients

continuing the LNG-IUS treatment resulting in higher compliance may also explain its better efficacy in treating endometrial hyperplasia compared with oral progestogens. The higher disease regression rate with LNG-IUS can reduce the number of hysterectomies performed for this condition and prevent progression to cancer.

In conclusion, although this review of observational studies found a lower chance of disease regression of endometrial hyperplasia with oral progestogens compared with LNG-IUS, it should be acknowledged that observational studies are fraught with potential biases and confounders. Our systematic examination of the published literature confirms the scarcity of high-quality evidence to reliably inform clinical practice in this area. Although the differences between oral progestogens and LNG-IUS may be seen as significant, these data should be interpreted with caution. This is because the studies are of observational design with mostly indirect comparisons between these 2 methods. In the absence of randomized studies with at least 5 years follow-up, (this review only had 2 studies with over 5 years follow-up data) the efficacy of oral progestogens and LNG-IUS remains in doubt. Our review should aid the design of a prospective, adequately powered, controlled trial to assess the short- and long-term effects of these interventions. A well-designed randomized controlled trial is therefore needed to address this question and generate the best evidence overcoming the pitfalls of observational studies. ■

ACKNOWLEDGMENT

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